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ORIGINAL ARTICLE

Mefenamic acid based novel indole analogues: Their synthesis and anti-proliferative effects

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Abstract Prompted by the literature report on anticancer properties of mefenamic acid, a series of mefenamic acid based indole derivatives were designed via a rational approach. Synthesis of this class of compounds was carried out via a 3-step method starting from the mefenamic acid and using the Pd/C–Cu mediated coupling-cyclization strategy as a key step. A focused library of related molecules was synthesized and evaluated for their anti-proliferative properties against normal (HEK293T) and oral (CAL 27) as well as breast (MCF-7) cancer cell lines when several compounds showed selective growth inhibition of oral cancer cells of which the compound **5g** [i.e. *N*-(2-(((5-fluoro-1-(methylsulfonyl)-1*H*-indol-2-yl)methoxy)methyl)phenyl)-2,3-dimethylaniline] was found to be promising.

1. Introduction

Among the various types of cancer, head and neck squamous cell carcinoma (HNSCC) including oral squamous cell carcinoma (OSCC) has emerged as the 6th most common malignancy worldwide (Pentenero et al., 2005; Chen et al., 2004). While reports suggest that more than 90% of oral cancer belongs to OSCC class, the diagnosis of this disease is often managed poorly (Funk et al., 2002; Muir and Weiland, 1995). For example, in spite of the availability of several treatment options including surgery, radiation and multi-drug chemotherapy, no significant rise of long-term survival for HNSCC patients has been observed in the recent past. Additionally, the unwanted side effects associated with the existing therapies and their unsatisfactory therapeutic actions at the end stage of the disease underline the need of better and new chemotherapeutic agents. Thus the discovery of novel small molecules as potential antiproliferative/cytotoxic agents not only is the essential need but also considered as an important approach to target HNSCC. In spite of posing considerable challenges this approach attracted enormous attention of medicinal/organic chemists.

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Several studies have indicated that non-steroidal anti-inflammatory drugs (NSAIDs) induce apoptosis in colon (Hara et al., 1997; Richter et al., 2001; Thun et al., 1993, 1991), breast (Harris et al., 1996), prostate (Hsu et al., 2000), and stomach (Sawaoka et al., 1998) cancer cells. For example, mefenamic acid (A, Fig. 1), a well known member of NSAIDs has been reported to show anti-proliferative effects as well as apoptosis when tested against human liver cancer cell lines (Woo et al., 2004). These reports prompted us to explore mefenamic acid as a potential starting point for the identification of new anti-proliferative agents. Due to the known anticancer properties (Jacquemard et al., 2008; Prasad et al., 2010; Tabata et al., 1993), 2-substituted indoles also attracted our attention. For example, an indole based derivative that is 4-(5-(1*H*-indol-2-yl)pyridin-3-yl)phenol has been identified as a CDK inhibitor as well as cytotoxic agent (Jacquemard et al., 2008) whereas indoles B (Fig. 1) containing a $-CH_2OCH-$ linker at C-2 position have shown anticancer properties (Prasad et al., 2010). Thus the integration of structural features of mefenamic acid A and indole B in a single molecular entity may afford a new template C (Fig. 1) for the identification of novel antiproliferative agents. Prompted by this idea and due to our interest in novel anticancer agents we constructed a focused library of small molecules based on C for *in vitro* screen. Herein, we report the Pd/C-mediated direct synthesis of mefenamic acid based several novel indole analogues via a coupling-cyclization strategy (Scheme 1) and their cytotoxic effects against oral cancer cells. To the best of our knowledge any earlier efforts toward the synthesis of this class of compounds and their pharmacological evaluation is not known in the literature.

Due to their occurrences in nature and a wide range of pharmacological properties, synthesis of indole has been a topic of extensive research over the years (Humphrey and Kuethe, 2006; Cacchi and Fabrizi, 2005; Gribble, 1996; Tabata et al., 1993; Krüger et al 2008; Ackermann 2007) Among the various methods reported toward the synthesis of 2-substituted indoles, those catalyzed by transitional metals have attracted particular attention. Not surprisingly, the palladium catalyzed reactions occupied the center stage because of their versatility, functional group tolerance and milder reaction conditions. A broad range of Pd catalysts have been employed for the synthesis of 2-substituted indoles. As a less expensive catalyst system Pd/C-based catalyst for example Pd/C–CuI–PPh_3 has gained considerable interest for the efficient synthesis of various heterocyclic structures (Pal, 2009) including indoles (Pal et al., 2004; Layek et al., 2009; Alinakhi et al., 2011; Rao et al., 2011). The catalyst Pd/C is stable and easy to handle as well as separable from the product. Thus, we decided to explore this Pd/C based coupling–cyclization strategy leading to indoles for accessing our target compounds based on **C** (Fig. 1). In order to expedite this strategy we required to synthesize the appropriate starting material that is the terminal alkyne necessary for our synthesis (Scheme 1). Accordingly, the carboxylic acid moiety of mefenamic acid (**1**) was reduced in the presence of $LiAlH_4$ to give the corresponding alcohol (Babu et al., 2014) **2** which on treatment with propargyl bromide in the presence of NaH afforded the expected terminal alkyne **3** (Scheme 2).

2. Materials and methods

2.1. General

Unless stated otherwise, reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (100–200 and 230–400 mesh) using hexane, ethyl acetate, dichloromethane. ^1H and ^{13}C NMR spectra were recorded either in $CDCl_3$ or in DMSO-d_6 solution by using a Varian 400 MHz spectrometer. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a JASCO FT-IR 4200 spectrometer. Melting points were determined using a POLMON melting point apparatus and are uncorrected. MS spectra were obtained on an AGILENT-6430 LC-MS/MS-Quadruple spectrometer.

2.2. Preparation of (2-(2,3-dimethylphenylamino)phenyl)methanol (2)

To a mixture of compound **1** (8.0 g, 33.1 mmol) in dry THF (50 mL), was added lithium aluminum hydride (LAH) (2.0 g, 49 mmol) at 0 °C under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction (indicated by TLC), the excess of LAH was quenched by adding ice (2 g) portion wise. The mixture was then extracted with ethyl acetate (3×15 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel (230–400 mesh) using 20% ethyl acetate/*n*-hexane to give desired compound **2** (yield 92%); yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21–7.17 (m, 2H), 7.11–7.04 (m, 2H), 6.99 (d, $J = 8.8$ Hz, 1H), 6.89 (d, $J = 6.8$ Hz, 1H), 6.82 (t, $J = 7.6$ Hz, 1H), 6.35 (s, 1H), 4.75 (s, 2H), 2.34 (s, 3H), 2.16 (s, 3H), 1.82 (s, 1H); MS (CI): 227.8 (M + 1).

2.3. Preparation of 2,3-dimethyl-N-(2-((prop-2-ynyloxy)methyl)phenyl)aniline (3)

Propargyl bromide (19.2 mmol) was added to a solution of (2-(2,3-dimethylphenylamino)phenyl)methanol (16 mmol) and

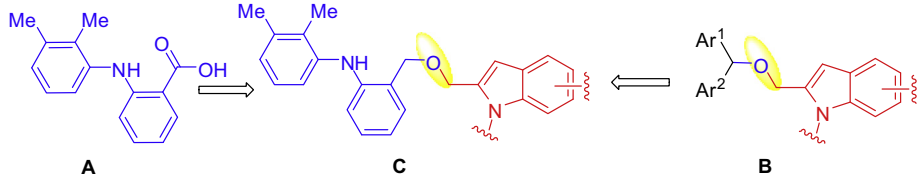
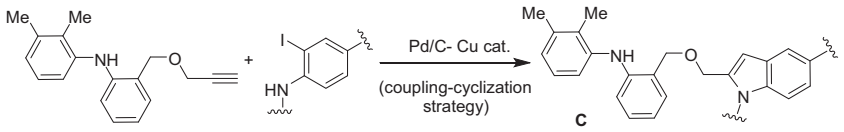
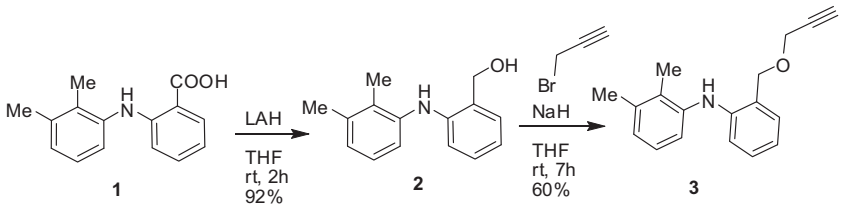


Figure 1 Design of mefenamic acid based novel anti cancer small molecules.



Scheme 1 Pd/C-mediated synthesis of mefenamic acid based novel indole derivatives (**C**) via a coupling-cyclization strategy.



Scheme 2 Synthesis of 2,3-dimethyl-*N*-(2-((prop-2-ynyloxy)methyl)phenyl)aniline (**3**).

sodium hydride (32 mmol) in THF (20 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 7 h. After completion of the reaction (confirmed by TLC), the mixture was diluted with ice water (60 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The residue was purified by column chromatography using hexane/ethyl acetate as a eluent to afford the title compound as a liquid; yield: 60%, Liquid, R_f = 0.3 (40% EtOAc-*n*-Hexane); IR (KBr) ν_{max}: 3464, 2930, 1835, 2230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.22 (ddd, J = 16.3, 11.7, 4.7 Hz, 2H), 7.14 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.03–6.99 (m, 1H), 6.90 (d, J = 7.2 Hz, 1H), 6.82 (dt, J = 7.3, 1.08 Hz, 1H), 6.70 (s, 1H), 4.72 (s, 2H), 4.22 (d, J = 2.3 Hz, 2H), 2.50 (t, J = 2.3 Hz, 1H), 2.35 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.7, 140.4, 137.9, 130.8, 129.6, 128.0, 125.8, 124.3, 122.8, 118.9, 118.4, 115.3, 75.1, 71.5, 70.8, 56.9, 20.7, 13.5; MS (ES mass): m/z 266 (M + 1, 100%).

2.4. General procedure for the preparation of compound ***(5)***

A mixture of iodo compound **4** (1 equiv), 10% palladium carbon (0.016 equiv.), triphenylphosphine (0.125 equiv.), cuprous iodide (0.02 equiv.) and triethylamine (2 equiv.) in methanol (5 mL) was stirred for 30 min under nitrogen atmosphere. To this mixture was added alkyne **3** (1 equiv) slowly and the mixture was refluxed for 4–8 h. After completion of the reaction (indicated by TLC) the mixture was then cooled to room temperature, filtered through celite, and methanol was removed under reduced pressure. The residue was diluted with water (50 mL) and extracted with ethyl acetate (3 × 25 mL). The organic layers were collected, combined, washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue thus obtained was purified by column chromatography to afford the desired compound.

2.5. 2,3-Dimethyl-N-(2-(((1-(methylsulfonyl)-1H-indol-2-yl)methoxy)methyl)phenyl)aniline ***(5a)***

Yield: 65%; Brown liquid; R_f = 0.2 (40% EtOAc-*n*-Hexane); IR (KBr) ν_{max}: 3338, 2924, 1580, 1360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.25–7.16 (m, 2H), 7.06 (td, J = 15.1, 7.4 Hz, 2H), 6.94 (d, J = 8.1 Hz, 1H), 6.89 (d, J = 6.9 Hz, 1H), 6.81 (t, J = 7.3 Hz, 1H), 6.69 (s, 1H), 6.64 (s, 1H), 4.85 (s, 2H), 4.73 (s, 2H), 3.15 (s, 3H), 2.30 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 140.4, 137.9, 137.0, 136.2, 130.5, 129.4, 128.4 (2C), 125.9, 125.2, 124.5, 123.6, 123.4, 121.2, 118.9, 118.8, 115.3, 113.9, 111.7, 71.8, 64.4, 41.0, 20.7, 13.6; MS (CI): 435 (M + 1, 100%); HPLC: 99%, Column: Symmetry C-18 75 * 4.6 mm 3.5 µm, mobile phase A: 0.1% TFA in water, mobile phase B: ACN (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min, UV 210 nm, retention time 5.2 min.

2.6. 2,3-Dimethyl-N-(2-(((1-tosyl-1H-indol-2-yl)methoxy)methyl)phenyl)aniline ***(5b)***

Yield: 70%; White solid; mp 110 °C, R_f = 0.2 (35% EtOAc-*n*-Hexane); IR (KBr) ν_{max}: 3386, 2942, 1586, 1353 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.3 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.27–7.17 (m, 3H), 7.06 (d, J = 7.2 Hz, 4H), 6.99 (t, J = 10.8 Hz, 1H), 6.93–6.83 (m, 2H), 6.71 (d, J = 10.7 Hz, 2H), 4.96 (s, 2H), 4.72 (s, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 144.9, 144.6, 140.6, 137.7, 137.0, 136.8, 135.7, 130.4, 129.5 (2C), 129.2, 128.8, 128.2, 126.7 (2C), 125.7, 124.8, 124.2, 123.6, 123.4, 120.9, 118.8, 118.6, 115.3, 114.5, 111.4, 71.8, 64.7, 21.4, 20.6, 13.5. MS (CI): 511.3 (M + 1, 100%); HPLC: 99.6%, Column: X-Terra C-18 250 * 4.6 mm, 5 µm, mobile phase A: 5 mm Ammonium acetate in water, mobile phase B: ACN (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min, Diluent: ACN: WATER (50:50) UV 210 nm, retention time 15.7 min.

2.7. 2,3-Dimethyl-N-(2-(((5-methyl-1-(methylsulfonyl)-1H-indol-2-yl)methoxy)methyl)phenyl) aniline ***(5c)***

Yield: 65%; White Solid; mp 136 °C, R_f = 0.35 (40% EtOAc-*n*-Hexane); IR (KBr) ν_{max}: 3379, 2925, 1587, 1357 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.5 Hz, 1H), 7.38 (s, 1H), 7.22–7.18 (m, 3H), 7.09–7.05 (m, 2H), 6.95–6.93 (m, 2H), 6.83 (t, J = 7.2 Hz, 1H), 6.65-6.62 (m, 2H), 4.84 (s,

2H), 4.74 (s, 2H), 3.14 (s, 3H), 2.47 (s, 3H), 2.33 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 140.5, 137.9, 136.2, 135.3, 133.2, 130.5, 129.4, 128.7, 128.4, 126.6, 125.9, 124.5, 123.4, 121.1, 118.9 (2C), 115.2, 113.6, 111.6, 71.8, 64.4, 40.8, 21.2, 20.7, 13.7; MS (CI): 449.1 (M + 1, 100%); HPLC: 99.5%, Column: Symmetry C-18 75 * 4.6 mm 3 µm, mobile phase A: 0.1% TFA in water, mobile phase B: ACN (T/%B): 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min, UV 260 nm, retention time 5.1 min.

2.8. 2,3-Dimethyl-N-(2-(((5-methyl-1-tosyl-1H-indol-2-yl)methoxy)methyl)phenyl)aniline ***(5d)***

Yield: 70%; Light yellow solid; mp 145 °C, R_f = 0.4 (40% EtOAc-*n*-Hexane); IR (KBr) v_{max}: 3338, 2927, 1580, 1370, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 4.2 Hz, 1H), 7.25–7.10 (m, 3H), 7.06–6.97 (m, 4H), 6.95 (d, J = 8.0 Hz, 1H), 6.89–6.80 (m, 2H), 6.69 (s, 1H), 6.60 (s, 1H), 4.91 (s, 2H), 4.69 (s, 2H), 2.41 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H),1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 144.6, 140.6, 137.8, 136.8, 135.8, 135.3, 133.1, 130.5, 129.5 (2C), 129.2, 129.1, 128.3, 126.7 (2C), 126.2, 125.8, 124.2, 123.7, 120.8, 118.8, 118.7, 115.3, 114.2, 111.4, 71.8, 64.7, 21.4, 21.2, 20.6, 13.5; MS (CI): 525.2 (M + 1, 100%); HPLC: 92.3%, Column: X-Terra C-18 250 * 4.6 mm, 5 µm, mobile phase A: 5 mm Ammonium acetate in water, mobile phase B: ACN (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min, Diluent: ACN: WATER (50:50) UV 210 nm, retention time 15.9 min.

2.9. N-(2-(((5,7-Dimethyl-1-(methylsulfonyl)-1H-indol-2-yl)methoxy)methyl)phenyl)-2,3-dimethylaniline ***(5e)***

Yield: 68%; Semi solid; R_f = 0.4 (50% EtOAc-*n*-Hexane); IR (KBr) v_{max}: 3391, 2926, 1610, 1473 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.19–7.15 (m, 3H), 7.08-7.01 (m, 2H), 6.97 (s, 1H), 6.97–6.86 (m, 2H), 6.79 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 10.6 Hz, 2H), 4.85 (s, 2H), 4.67 (s, 2H), 3.11 (s, 3H), 2.64 (s, 3H), 2.39 (s, 3H), 2.29 (s, 3H), 2.04 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 140.4, 139.4, 137.8, 136.4, 134.0, 131.5, 130.5, 130.4, 129.3, 128.4, 126.1, 125.8, 124.4, 123.4, 118.9, 118.8 (2C), 115.2, 114.1, 71.6, 66.1, 40.7, 22.1, 20.8, 20.6, 13.5; MS (CI): 463.0 (M + 1, 100%); HPLC: 97%, Column: Symmetry C-18 75 * 4.6 mm 3.5 µm, mobile phase A: 0.1% TFA in water, mobile phase B: ACN (T/%B): 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min, UV 260 nm, retention time 5.2 min.

2.10. N-(2-(((5,7-Dimethyl-1-tosyl-1H-indol-2-yl)methoxy)methyl)phenyl)-2,3-dimethylaniline ***(5f)***

Yield: 60%; Brown liquid; R_f = 0.35 (40% EtOAc-*n*-Hexane); IR (KBr) v_{max}: 3380, 2927, 1796,, 1226 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 8.3 Hz, 2H), 7.21–7.15 (m, 2H), 7.05–7.00 (m, 5H), 6.94–6.90 (m, 2H), 6.90–6.86 (m, 1H), 6.80 (dt, J = 7.3, 1.07 Hz, 1H), 6.66 (s, 1H), 6.60 (s, 1H), 4.88 (s, 2H), 4.69 (s, 2H), 2.57 (s, 3H), 2.35–2.32 (m, 3H), 2.29 (s, 3H), 2.28 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9 144.1, 140.6, 140.4, 137.7, 137.2, 135.1, 134.3, 132.6, 130.4, 130.3, 129.2 (2C), 128.4, 127.6, 126.2 (2C), 125.7, 124.2, 123.7, 118.8, 118.7 (2C), 115.2 (2C), 114.2, 71.9, 66.3, 22.0, 21.5, 20.9, 20.6, 13.6; MS (CI): 539.1 (M + 1, 100%); HPLC: 90%, Column: Symmetry C-18 75 * 4.6 mm 3.5 µm, mobile phase A: 0.1% TFA in water, mobile phase B: ACN (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min, UV 210 nm, retention time 5.7 min.

2.11. N-(2-(((5-Fluoro-1-(methylsulfonyl)-1H-indol-2-yl)methoxy)methyl)phenyl)-2,3-dimethylaniline ***(5g)***

Yield: 68%; Light yellow solid; mp 110–112 °C; R_f = 0.3 (45% EtOAc-*n*-Hexane); IR (KBr) v_{max}: 3382, 2930, 1592, 1363 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (dd, J = 9.1, 4.3 Hz, 1H), 7.25–7.17 (m, 3H), 7.08–7.05 (m, 3H), 6.97–6.88 (m, 2H), 6.82–6.79 (m, 1H), 6.65 (s, 1H), 6.58 (s, 1H), 4.83 (s, 2H), 4.74 (s, 2H), 3.14 (s, 3H), 2.31 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8 (d, C–F J = 239.1), 144.8, 140.4, 137.8 (d, C–F J = 8.2), 133.3, 130.5, 129.5, 129.4 (d, C–F J = 10.1), 128.3, 125.8, 124.5, 123.2, 118.9, 118.8, 115.3 (d, C–F J = 9.0), 113.2 (d, C–F J = 25.2), 111.3, 111.2, 109.9, 106.7 (d, C–F J = 23.8), 71.9, 64.3, 41.1, 20.7, 13.6; MS (CI): 453 (M + 1, 100%); HPLC: 97.7%, Column: Symmetry C-18 75 * 4.6 mm 3.5 µm, mobile phase A: 0.1% TFA in water, mobile phase B: ACN (T/%B): 0/20, 1/20, 6/98, 10/98, 12/20, 15/20; flow rate: 1.0 mL/min, UV 210 nm, retention time 7.8 min.

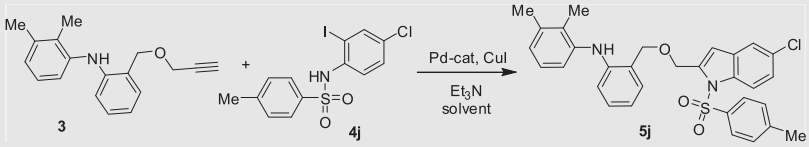
2.12. N-(2-(((5-Fluoro-1-tosyl-1H-indol-2-yl)methoxy)methyl)phenyl)-2,3-dimethylaniline ***(5h)***

Yield: 70%; White solid; mp 104–106 °C; R_f = 0.4 (40% EtOAc-*n*-Hexane); IR (KBr) v_{max}: 3387, 2948, 1596, 1353, 1262 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, J = 9.1, 4.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.23–7.16 (m, 2H), 7.13 (dd, J = 8.5, 2.5 Hz, 1H), 7.09–6.98 (m, 5H), 6.94 (d, J = 7.9 Hz, 1H), 6.85–6.87 (m, 2H), 6.63 (d, J = 4.5 Hz, 2H), 4.91 (s, 2H), 4.70 (s, 2H), 2.27 (s, 3H), 2.28 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8 (d, C–F J = 239.0), 144.9 (2c), 140.5, 138.6 (d, C–F J = 86.7), 135.5, 130.5, 129.9 (d, C–F J = 10.0) 129.6 (2C), 129.3, 128.3, 126.7 (2C), 125.8, 124.3, 123.5, 118.8, 118.7, 115.6 (d, C–F J = 9.2), 115.3, 112.8 (d, C–F J = 30.0), 112.5, 111.0 (2C), 106.5 (d, C–F J = 23.7), 71.9, 64.7, 21.4, 20.6, 13.5; MS (CI): 528.2 (M + 1, 100%); HPLC: 99.6%, Column: X-Terra C-18 250 * 4 mm, 5 µm, mobile phase A: 5 mm Ammonium acetate in water, mobile phase B: ACN (T/%B): 0/20, 3/20, 6/98, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min, Diluent: ACN: WATER (50:50) UV 210 nm, retention time 16.0 min.

2.13. N-(2-(((5-Chloro-1-(methylsulfonyl)-1H-indol-2-yl)methoxy)methyl)phenyl)-2,3-dimethylaniline ***(5i)***

Yield: 65%; Light green solid; mp 110 °C, R_f = 0.25 (40% EtOAc-*n*-Hexane); IR (KBr) v_{max}: 3369, 2931, 1594, 1375 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.9 Hz, 1H), 7.55 (d, J = 1.5 Hz, 1H), 7.37–7.27 (m, 3H), 7.26–7.16 (m, 2H), 6.95–6.90 (m, 2H), 6.82 (t, J = 7.3 Hz, 1H), 6.63 (s, 1H), 6.57 (s, 1H), 4.82 (s, 2H), 4.73 (s, 2H), 3.15 (s, 3H), 2.30 (s, 3H), 2.06 (s, 3H); ^{13}C NMR

Table 1 Effect of reaction conditions on coupling of terminal alkyne **3** with **4j**[a].



Entry	Pd-catalyst	Base	Time	Yield[b]
1.	10% Pd/C-PPh_3	Et_3N	5	70
2.	10% Pd/C-PPh_3	Et_3N	7	80
3.	10% Pd/C-PPh_3	Et_3N	9	65
4.	$Pd(OAc)_2$	Et_3N	7	42
5.	PPh_3	Et_3N	7	17
6.	No catalyst	Et_3N	2	No reaction
7.	10% Pd/C-PPh_3	K_2CO_3	7	46

[a] All reactions were carried out using alkyne **3** (1 equiv.), **4j** (1 equiv.), a Pd-catalyst (0.016 equiv.), PPh_3 (0.125 equiv.), CuI (0.02 equiv.), and Et_3N (2 equiv.) in MeOH (5.0 mL) at 65 °C.
[b] Isolated yields.

(100 MHz, $CDCl_3$): δ 144.8, 140.4, 137.9, 137.6, 135.3, 133.8, 130.5, 129.5, 129.3, 128.6, 125.9, 125.3, 124.5, 123.2, 120.7, 118.9, 118.8, 115.3, 115.0, 110.7, 72.0, 64.3, 41.2, 20.7, 13.6; MS (CI): 469.1 (M^+, 100%), 571.2 (M + 2, 33%); HPLC: 97.5%, Column: Symmetry C-18 75 * 4.6 mm 3.5 µm, mobile phase A: 0.1% TFA in water, mobile phase B: ACN (T/%B): 0/20, 0.5/20, 2/95, 8/95, 10/20, 12/20; flow rate: 1.0 mL/min, UV 210 nm, retention time 5.8 min.

2.14. N-(2-(((5-Chloro-1-tosyl-1H-indol-2-yl)methoxy)methyl)phenyl)-2,3-dimethylaniline ***(5j)***

Yield: 80%; White solid; R_f = 0.35 (35% EtOAc-*n*-Hexane); IR (KBr) ν_{max}: 3309, 2943, 1603, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.9 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 1.9 Hz, 1H), 7.30 (dd, *J* = 9.3, 2.50 Hz, 1H), 7.22 (dd, *J* = 13.0, 6.9 Hz, 2H), 7.05 (td, *J* = 7.7, 6.7 Hz, 4H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.92–6.82 (m, 2H), 6.64 (s, 2H), 4.93 (s, 2H), 4.72 (s, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 144.9, 140.5, 138.4, 137.8, 135.4, 135.3, 130.5, 130.1, 129.6 (2C), 129.3, 129.2, 128.2, 126.7 (2C), 125.8, 124.9, 124.3, 123.5, 120.4, 118.8, 118.7, 115.5, 115.3, 110.4, 72.0, 64.6, 21.4, 20.6, 13.5; MS (CI): 545.1 (M^+, 100%), 547.2 (M + 2, 32%); HPLC: 99.5%, Column: X-Terra C-18 250 * 4.6 mm, 5 µm, mobile phase A: 5 mm Ammonium acetate in water, mobile phase B: ACN (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min, Diluent: ACN: WATER (50:50) UV 210 nm, retention time 16.1 min.

2.15. N-(2-(((5-Bromo-1-(methylsulfonyl)-1H-indol-2-yl)methoxy)methyl)phenyl)-2,3-dimethylaniline ***(5k)***

Yield: 75%; White solid; mp 140 °C, R_f = 0.32 (30% EtOAc-*n*-Hexane); IR (KBr) ν_{max}: 3379, 2927, 1587, 1356, 1322 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 7.45 (dd, *J* = 8.9, 1.90 Hz, 1H), 7.23–7.17 (m, 2H), 7.11–7.02 (m, 2H), 6.97–6.88 (m, 2H), 6.82 (t, *J* = 7.3 Hz, 1H), 6.63 (s, 1H), 6.56 (s, 1H), 4.83 (s, 2H), 4.74 (s, 2H), 3.15 (s, 3H), 2.31 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 140.4, 137.9, 137.5, 135.7, 130.5, 130.1, 129.5, 128.3, 128.0, 125.9, 124.6, 123.8, 123.2, 119.0, 118.9, 116.9, 115.4 (2C), 110.6, 72.0, 64.2, 41.2, 20.6, 13.6; MS (CI): 513.1 (M^+, 100%), 515.2 (M + 2, 95%); HPLC: 99.3%, Column: X-Terra C-18 250 * 4.6 mm, 5 µm, mobile phase A: 5 mm Ammonium acetate in water, mobile phase B: ACN (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min, Diluent: ACN: WATER (50:50) UV 230 nm, retention time 15.7 min.

2.16. N-(2-(((5-Bromo-1-tosyl-1H-indol-2-yl)methoxy)methyl)phenyl)-2,3-dimethylaniline ***(5l)***

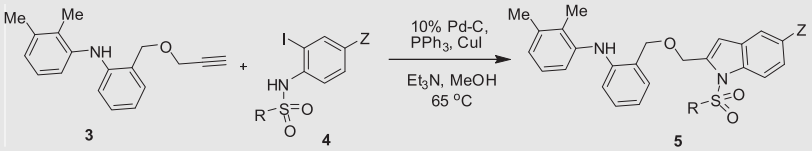
Yield: 70%; White solid; mp 148 °C, R_f = 0.45 (40% EtOAc-*n*-Hexane); IR (KBr) ν_{max}: 3387, 2927, 1594, 1354 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.01 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.41 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.19 (dd, *J* = 13.5, 7.2 Hz, 2H), 7.10–6.98 (m, 4H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.90–6.79 (m, 2H), 6.61 (s, 2H), 4.90 (s, 2H), 4.69 (s, 2H), 2.28 (s, 3H), 2.26 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 144.9, 140.5, 138.2, 137.8, 135.7, 135.4, 130.6, 130.5, 129.6 (2C), 129.3, 128.2, 127.6, 126.7 (2C), 125.8, 124.3, 123.5 (2C), 118.8, 118.6, 116.8, 115.9, 115.3, 110.2, 72.0, 64.5, 21.4, 20.6, 13.5; MS (CI): 588.1 (M^+, 100%), 590.2 (M + 2, 95%); HPLC: 99.4%, Column: X-Terra C-18 250 * 4.6 mm, 5 µm, mobile phase A: 5 mm Ammonium acetate in water, mobile phase B: ACN (T/%B): 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min, Diluent: ACN: WATER (50:50) UV 210 nm, retention time 16.8 min.

2.17. Cell proliferation assay

The anti-proliferative activity and cancer cell selectivity of the synthesized compounds on normal and cancer cells were evaluated using the SRB (Sulforhodamine B) cell proliferation assay.

In brief, the assay was performed as follows: Cal 27 (oral cancer cell line), MCF-7 (breast cancer cell line) and non-cancer [Human Embryonic Kidney (HEK) 293T cell line] cells

Table 2 Synthesis of mefenamic acid based indole derivatives (5)[a].



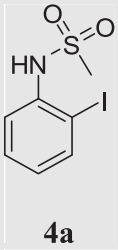
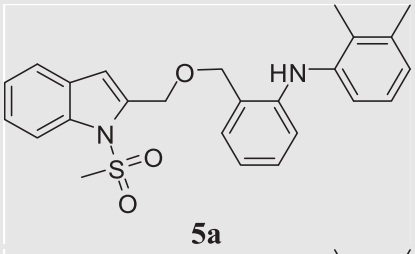
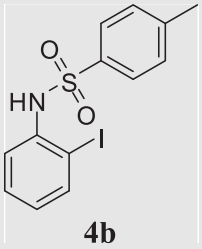
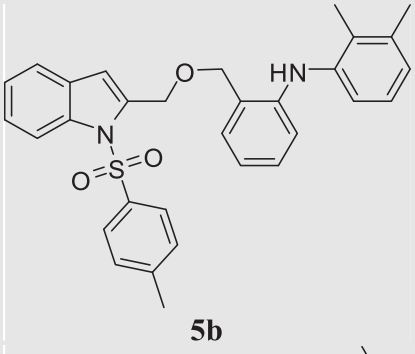
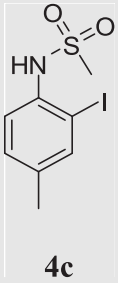
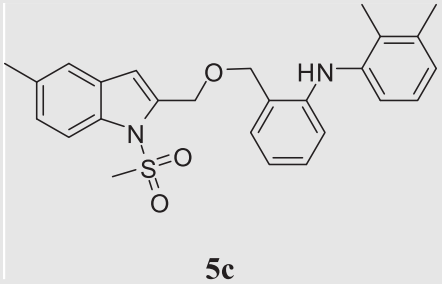
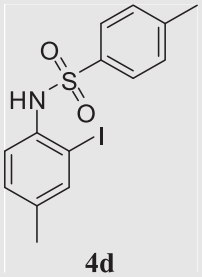
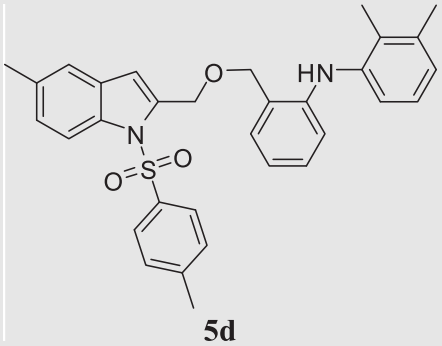
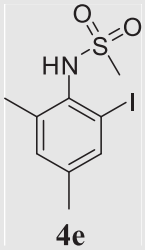
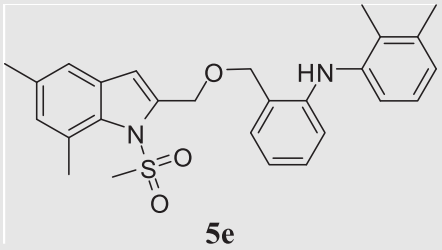
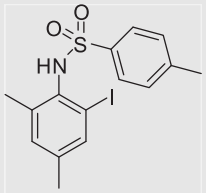
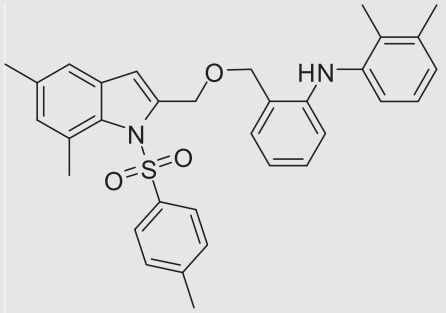
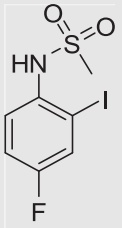
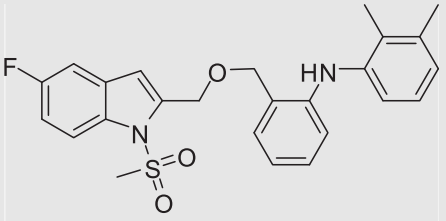
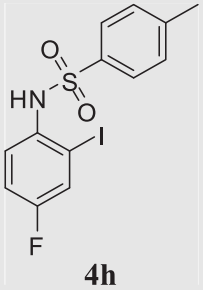
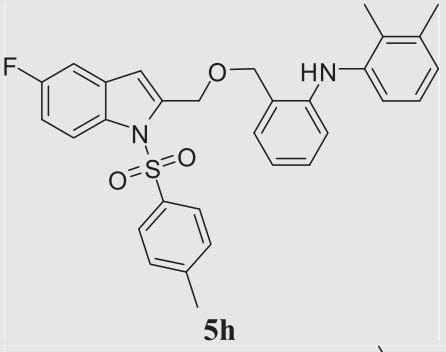
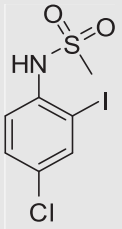
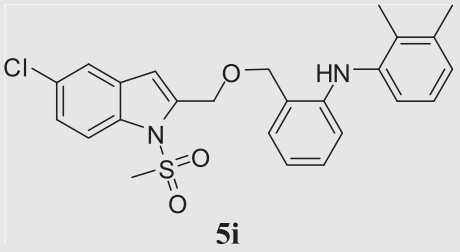
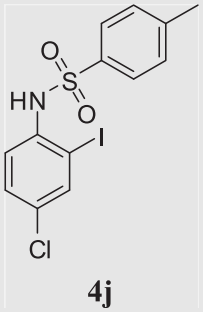
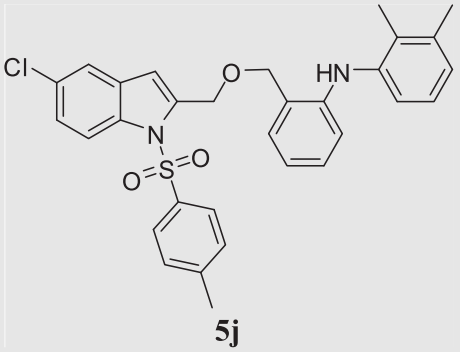
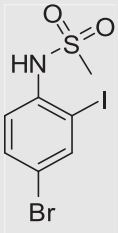
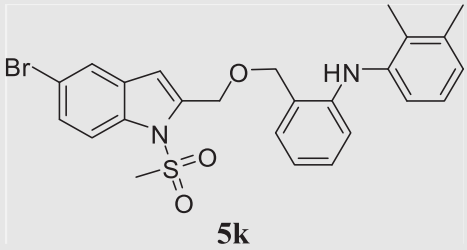
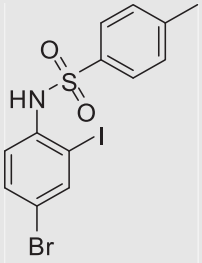
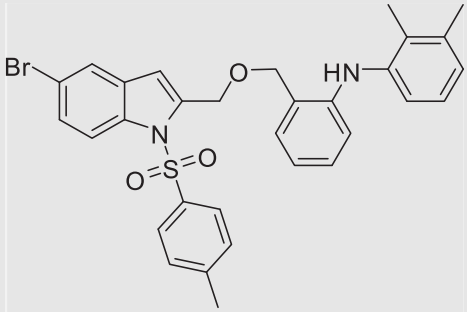
Entry	*o*-Iodoanilide (**4**)	Products[b] (**5**)	Time (h)	Yield[c] (%)
1	 **4a**	 **5a**	5	65
2	 **4b**	 **5b**	4.5	70
3	 **4c**	 **5c**	4	65
4	 **4d**	 **5d**	5	70
5	 **4e**	 **5e**	6	68

Table 2 (*continued*)

Entry	*o*-Iodoanilide (**4**)	Products[b] (**5**)	Time (h)	Yield[c] (%)
6	 **4f**	 **5f**	6	60
7	 **4g**	 **5g**	6.5	68
8	 **4h**	 **5h**	7	70
9	 **4i**	 **5i**	8	65
10	 **4j**	 **5j**	**7**	80

(*continued on next page*)

Table 2 (*continued*)

Entry	*o*-Iodoanilide (**4**)	Products[b] (**5**)	Time (h)	Yield[c] (%)
11	 **4k**	 **5k**	6	75
12	 **4l**	 **5l**	6.5	70

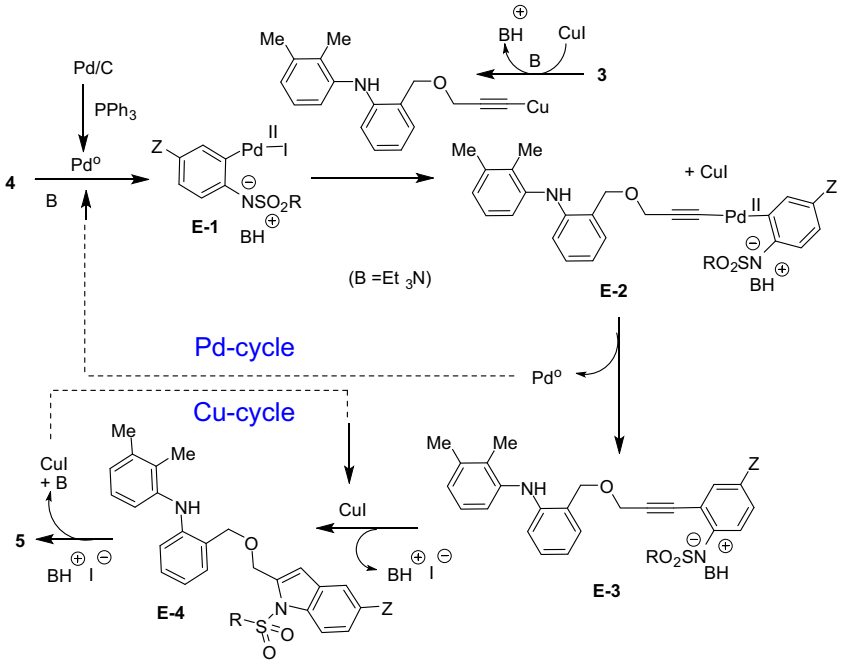
[a] All the reactions were carried out using alkyne **3** (1 equiv.), **4** (1 equiv.), 10% Pd/C (0.016 equiv.), PPh_3 (0.125 equiv.), CuI (0.02 equiv.), and Et_3N (2 equiv.) in MeOH at 65 °C.
[b] Identified by ^1H and ^{13}C NMR, IR, and MS.
[c] Isolated yields.

were seeded in 96-well plates and incubated overnight. The optimum cell numbers to be seeded were determined by a growth curve analysis for each cell line. In the initial (single dose) screen, compounds (dissolved in 100% DMSO to a stock concentration of 100 mM) were added to the adhered cells at a final concentration of 10 μM. After 72 h of treatment, the cells were washed with phosphate-buffered saline and ice-cold 10% trichloroacetic acid was added to the cells to precipitate all proteins for 1 h at 4 °C. The cells were then washed with water and air-dried. Cellular proteins were then stained using 0.4% SRB solution in 1% acetic acid for 10 min at room temperature. The unbound dye was washed away by destaining with 1% acetic acid and bound dye solubilized with 10 μM Tris solution. Absorbance of solubilized dye was measured at a wavelength of 590 nm. Percentage growth was determined by the formula [(At–A0/Ac–A0)] X 100, where At = absorbance after 72 h of test compound treatment, A0 = Absorbance at time 0, Ac = Absorbance after 72 h without treatment.

3. Results and discussion

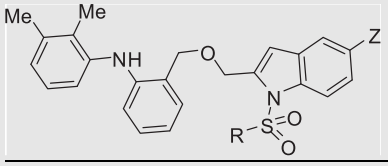
3.1. Chemistry

In order to establish the optimized reaction conditions, the Pd/C-mediated coupling of **3** with *N*-(4-chloro-2-iodophenyl)-4-methylbenzenesulfonamide (**4j**) was used as a model reaction (Table 1). Initially, this reaction was carried out in the presence of 10% Pd/C–PPh_3–CuI and Et_3N in MeOH at refluxing temperature (65 °C) for 5 h when the expected product **5j** was isolated in 70% yield (Table 1, entry 1). An increase of reaction time to 7 h however afforded **5j** in 80% yield (Table 1, entry 2). A further increase in reaction time to 9 h did not improve the product yield (Table 1, entry 3). In fact the yield was decreased in this case due to the partial decomposition of the product perhaps due to its prolonged exposure to Et_3N/MeOH under the refluxing conditions. The use of other catalyst, for example $Pd(OAc)_2$ afforded the product **5j** but in inferior yield under the conditions employed (Table 1, entry 4). The omission of Pd/C (Table 1, entry 5) was found to be less effective whereas the reaction did not proceed in the absence of 10% Pd/C–PPh_3–CuI catalyst system (entry 6, Table 1). While all these reactions were carried out using Et_3N as a base the use of an inorganic base for example K_2CO_3 was also examined. The reaction proceeded in this case affording the desired product **5j** but the yield was only 46% (Table 1, entry 7). Thus, 10% Pd/C–PPh_3–CuI in combination with Et_3N in MeOH was found to be optimal (Table 1, entry 2) and used to prepare other analogues of **5j**. A number of *o*-iodosulphanilides (**4a–l**) were reacted with the alkyne **3** under the optimized conditions (Table 2). The reactions proceeded well irrespective of the presence of groups such as Me, F, Cl, and Br on the anilide ring affording the desired indoles **5** in acceptable yields. All the indole derivatives (**5**) synthesized were characterized by spectral (NMR, IR and MS) data. The presence of indole ring was confirmed by the appearance of a singlet at ~6.6 δ due to the C-3 indole proton in the ^1H NMR spectra of **5**. The two singlets near ~4.9 and 4.7 δ indicated the presence of $–CH_2–O–CH_2–$ moiety.



Scheme 3 Proposed reaction mechanism for the Pd/C–Cu mediated synthesis of **5** via the coupling-cyclization strategy.

Table 3 The % of growth inhibition of cancer cells by compound **5** at 10 μM.

Compounds (**5**)	% inhibition[a]		
	CAL 27 (oral cancer)	MCF-7 (breast cancer)	HEK 293T
5a; R = Me, Z = H	2.78 ± 1.40	10.21 ± 1.03	9.21 ± 2.79
5c; R = Me, Z = Me	28.70 ± 5.11	31.96 ± 3.22	4.65 ± 0.91
5g; R = Me, Z = F	55.56 ± 6.05	2.67 ± 1.31	8.10 ± 1.12
5h; R = C_6H_4Me-*p*, Z = F	47.22 ± 4.98	2.71 ± 0.97	0.89 ± 0.56
5i; R = Me, Z = Cl	25.92 ± 5.23	10.63 ± 2.05	0.24 ± 0.12
5k; R = Me, Z = Br	12.99 ± 1.76	9.66 ± 1.56	9.66 ± 2.11
5l; R = C_6H_4Me-*p*, Z = Br	44.45 ± 6.53	0.75 ± 0.25	0.39 ± 0.09
Gemcitabine	78 ± 2.05	59.17 ± 1.21	22.70 ± 1.45

[a] Average of at least three determinations.

A proposed reaction mechanism for the present Pd/C-mediated synthesis of mefenamic acid based indole derivatives (**5**) is shown in Scheme 3. The reaction seemed to proceed via generation of an active Pd(0) species from Pd/C that actually catalyze the C–C bond forming reaction between **3** and **4**. Thus, the active Pd(0) species generated *in situ* (Prasad et al., 2012; Chen et al., 2007; Rambabu et al., 2013) (Scheme 3) undergoes oxidative addition with **4** to give **E-1**. The organo-Pd(II) species **E-1** then undergoes trans organometallation with copper acetylide generated *in situ* from CuI and **3** to afford **E-2.** Notably, CuI is regenerated during this step. The reductive elimination of Pd(0) from **E-2** completes the Pd-catalytic cycle and affords the internal alkyne **E-3.** In the next step **E-3** undergoes Cu-mediated intramolecular cyclization to give the desired product **5** via **E-4** with the regeneration of CuI. Overall, the whole process seemed to proceed via two catalytic cycles that is the Pd-cycle followed by a Cu-cycle.

3.2. Pharmacology

All the mefenamic acid based indole derivatives (**5**) synthesized were tested for their anti-proliferative properties and cancer cell selectivity against normal (Human Embryonic Kidney 293T or HEK293T) and oral (oral adenosquamous or CAL 27) as well as breast (MCF-7) cancer cell lines at 10 μM using a sulforhodamine B (SRB) assay. This assay was chosen because of its sensitivity, large dynamic range and the ability to measure cell proliferation over three days with normalization to initial cell number as well as vehicle-treated cells. Further, this is the assay of choice for anticancer compound screening at the National

Cancer Institute (NIH). The SRB assay provides a colorimetric readout which can be spectrophotometrically measured and does not involve the use of antibodies or toxic reagents. The assay is based on detection of total protein content of cells, which increases or decreases in proportion with cell number. Gemcitabine was used as a reference compound in this assay (Chu and DeVita, 2007). The results of representative compounds found to be active along with few less or not active compounds are presented in Table 3. The compounds **5g**, **5h** and **5l** were found to be active against oral cancer cells (Table 3) whereas the compound **5c** showed growth inhibition of breast cancer cells (Table 3). It is evident from this study that a fluorine substituent at the C-5 position of indole ring is beneficial (**5g** and **5h** vs rest of the compounds except **5l**) whereas a methanesulfonyl group at indole nitrogen is favored for growth inhibition against CAL27 cells (compound **5g** vs **5h**). However, the p-toluenesulfonyl group appeared to impart better selectivity than the methanesulfonyl group (compound **5h** and **5l** vs rest of the compounds). Notably, none of these compounds showed significant effect on HEK293T cells (Table 3) indicating their selectivity toward cancer cells especially oral cancer. While the exact reason for such observation is not clear at this stage, this kind of behavior of small organic molecules has been reported by several researchers in the literature earlier (Cui et al., 2015). Nevertheless, though **5h** and **5l** showed better selectivity, the compound **5g** was identified as the best anti-proliferative agent (~55% growth inhibition) among the compounds tested against oral cancer and therefore may be of further medicinal interest.

4. Conclusion

In conclusion, the concept of using mefenamic acid as a starting point for the identification of novel anti-proliferative agents has been explored in the present study. Thus a series of mefenamic acid based indole derivatives were designed via a rational approach. Their design was prompted by the literature report on anticancer properties of mefenamic acid. Synthesis of this class of compounds was carried out via a 3-step method starting from the mefenamic acid. The Pd/C–Cu mediated coupling-cyclization strategy leading to the construction of an indole ring was used as a key step when the desired mefenamic acid based indole derivatives were isolated in acceptable yields. A focused library of related molecules was synthesized and evaluated for their anti-proliferative properties against normal (HEK293T) and oral (CAL 27) as well as breast (MCF-7) cancer cell lines at 10 μM using a sulforhodamine B (SRB) assay. Several of these compounds showed selective growth inhibition of oral cancer cells of which the compound **5g** was found to be promising in terms of % growth inhibition and may be of further interest. In summary, our study indicated that the mefenamic acid based indole framework presented here could be an attractive template for the design of small molecules of potential pharmacological interest that could be accessed conveniently via a Pd/C–Cu catalyzed coupling-cyclization method.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2015.05.018.

References

Ackermann, L., 2007. Catalytic arylations with challenging substrates: from air-stable HASPO preligands to indole syntheses and C–H-bond functionalizations. Synlett, 507–526.

Alinakhi, Prasad, B., Reddy, U., Rao, R.M., Sandra, S., Kapavarapu, R., Rambabu, D., Krishna, G.R., Reddy, C.M., Ravada, K., Misra, P., Iqbal, J., Pal, M., 2011. A new route to indoles via in situ desilylation-Sonogashira strategy: identification of novel small molecules as potential anti tuberculosis agents. Med. Chem. Commun. 2, 1006–1010.

Babu, P.V., Mukherjee, S., Gorja, D.R., Yellanki, S., Medisetti, R., Kulkarni, P., Mukkanti, K., Pal, M., 2014. Zebrafish based strategy for the identification of potential pharmacophore for apoptosis: a greener CuAAC approach to novel 1,2,3-triazoles derived from mefenamic acid. RSC Adv. 4, 4878–4882.

Cacchi, S., Fabrizi, G., 2005. Synthesis and functionalization of indoles through palladium-catalyzed reactions. Chem. Rev. 105, 2873–2920.

Chen, Y.J., Lin, S.C., Kao, T., Chang, C.S., Hong, P.S., Shieh, T.M., Chang, K.W., 2004. Genome-wide profiling of oral squamous cell carcinoma. J. Pathol. 204, 326.

Chen, J.-S., Vasiliev, A.N., Panarello, A.P., Khinast, J.G., 2007. Pd-leaching and Pd-removal in Pd/C-catalyzed Suzuki couplings. Appl. Catal. A Gen. 325, 76–86.

Chu, E., DeVita, T.V., 2007. Physicians' Cancer Chemotherapy Drug Manual. Jones & Bartlett.

Cui, J., Qi, B., Gan, C., Liu, Z., Huang, H., Lin, Q., Zhao, D., Huang, Y., 2015. Synthesis and in vitro antiproliferative evaluation of some B-norcholesteryl benzimidazole and benzothiazole derivatives. Mar. Drugs 13, 2488–2504. http://dx.doi.org/10.3390/md13042488.

Funk, G.F., Karnell, L.H., Robinson, R.A., Zhen, W.K., Trask, D.K., Hoffman, H.T., 2002. Presentation, treatment, and outcome of oral cavity cancer: a National Cancer Data Base report. Head Neck 24, 165.

Gribble, G.W., 1996. In: Katrizky, A.R., Rees, C.W., Scriven, E.F.V. (Eds.) Comprehensive Heterocyclic Chemistry II. Pergamon: Oxford, vol. 2, p 20.

Hara, A., Yoshimi, N., Niwa, M., Ino, N., Mori, H., 1997. Apoptosis induced by NS-398, a selective cyclooxygenase-2 inhibitor, in human colorectal cancer cell lines. Jpn. J. Cancer Res. 88, 600–604.

Harris, R.E., Namboodiri, K.K., Farrar, W.B., 1996. Nonsteroidal antiinflammatory drugs and breast cancer. Epidemiology 7, 203–205.

Hsu, A.L., Ching, T.T., Wang, D.S., Song, X., Rangnekar, V.M., Chen, C.S., 2000. The cyclooxygenase-2 inhibitor celecoxib induces apoptosis by blocking Akt activation in human prostate cancer cells independently of Bcl-2. J. Biol. Chem. 275, 11397–11403.

Humphrey, G.R., Kuethe, J.T., 2006. Practical methodologies for the synthesis of indoles. Chem. Rev. 106, 2875–2911.

Jacquemard, U., Dias, N., Lansiaux, A., Bailly, C., Logé, C., Robert, J.M., Lozach, O., Meijer, L., Mérour, J.Y., Routier, S., 2008. Synthesis of 3,5-bis(2-indolyl)pyridine and 3-[(2-indolyl)-5-phenyl]-pyridine derivatives as CDK inhibitors and cytotoxic agents. Bioorg. Med. Chem. 16, 4932–4953.

Krüger, K., Tillack, A., Beller, M., 2008. Catalytic synthesis of indoles from alkynes. Adv. Synth. Catal. 350, 2153–2167.

Layek, M., Lakshmi, U., Kalita, D., Barange, D.K., Islam, A., Mukkanti, K., Pal, M., 2009. Pd/C-Mediated synthesis of indoles in

water. Beilstein J. Org. Chem. 5. http://dx.doi.org/10.3762/bjoc.5.46.

Muir, C., Weiland, L., 1995. Upper aerodigestive tract cancers. Cancer 75, 147.

Pal, M., 2009. Palladium-catalyzed alkynylation of aryl and hetaryl halides: a journey from conventional palladium complexes or salts to palladium/carbon. Synlett, 2896–2912, For a review, see.

Pal, M., Subramanian, V., Batchu, V.R., Dager, I., 2004. Synthesis of 2-substituted indoles via Pd/C catalyzed reaction in water. Synlett, 1965–1969.

Pentenero, M., Gandolfo, S., Carrozzo, M., 2005. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck 27, 1080–1091.

Prasad, S.B.B., Vinaya, K., Kumar, C.S.A., Swarup, S., Rangappa, K.S., 2010. Synthesis and in vitro antiproliferative activity of diphenyl(sulphonylpiperidin-4-yl)methanol derivatives Med. Chem. Res. 19, 220–235.

Prasad, B., Kumar, K.S., Babu, P.V., Anusha, K., Rambabu, D., Kandale, A., Vanaja, G.R., Kalle, A.M., Pal, M., 2012. $AlCl_3$ induced C–N bond formation followed by Pd/C-Cu mediated couplingcyclization strategy: synthesis of pyrrolo[2,3-b]quinoxalines as anticancer agents. Tetrahedron Lett. 53, 6059–6066.

Rambabu, D., Bhavani, S., Swamy, N.K., Rao, M.V.B., Pal, M., 2013. Pd/C-mediated depropargylation of propargyl ethers/amines in water. Tetrahedron Lett. 54, 1169–1173.

Rao, R.M., Reddy, U., Alinakhi, Mulakayala, N., Alvala, M., Arunasree, M.K., Poondra, R.R., Iqbal, J., Pal, M., 2011. Sequential coupling/desilylation-coupling/cyclization in a single pot under Pd/C–Cu catalysis: synthesis of 2-(hetero)aryl indoles. Org. Biomol. Chem. 9, 3808–3816.

Richter, M., Weiss, M., Weinberger, I., Furstenberger, G., Marian, B., 2001. Growth inhibition and induction of apoptosis in colorectal tumor cells by cyclooxygenase inhibitors. Carcinogenesis 22, 17–25.

Sawaoka, H., Kawano, S., Tsuji, S., Tsujii, M., Gunawan, E.S., Takei, Y., Nagano, K., Hori, M., 1998. Cyclooxygenase-2 inhibitors suppress the growth of gastric cancer xenografts via induction of apoptosis in nude mice. Am. J. Physiol. 274, G1061–G1067.

Tabata, N., Sunazuka, T., Tomoda, H., Nagamitsu, T., Iwai, Y., Omura, S., 1993. Diolmycins, new anticoccidial agents produced by Streptomyces sp. II. Structure elucidation of diolmycins A1, A2, B1 and B2, and synthesis of diolmycin A1. J. Antibiot. 46, 762–769.

Thun, M.J., Namboodiri, M.M., Heath Jr., C.W., 1991. Aspirin use and reduced risk of fatal colon cancer. N. Engl. J. Med. 325, 1593–1596.

Thun, M.J., Namboodiri, M.M., Calle, E.E., Flanders, W.D., Heath Jr., C.W., 1993. Aspirin use and risk of fatal cancer. Cancer Res. 53, 1322–1327.

Woo, D.H., Han, I.S., Jung, G., 2004. Mefenamic acid-induced apoptosis in human liver cancer cell-lines through caspase-3 pathway. Life Sci. 75, 2439–2449.

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